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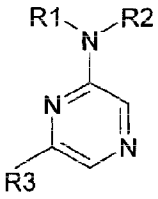
(54) Title: PHARMACEUTICAL COMPOUNDS



(I)

(57) Abstract: The invention provides a compound of the general formula (I) wherein R1 is selected from hydrogen, cycloalkyl and cycloalkenyl having 3 to 7 ring members; phenyl-C_{1-4} alkyl or a group R^4-A-CH_2- wherein R^4 is selected from amino, mono- or di-C_{1-4} alkylamino, hydroxyl, C_{1-4} alkoxy, SH, $SO_2NR^9R^9$, $CONR^9R^9$, $NR^9SO_2R^{10}$ and NR^9COR^{10}, and A is a C_{1-4} alkylene chain or a group - $(CH_2)_m$-B-$(CH_2)_n$- wherein m and n are each independently 0, 1 or 2 and B is a divalent cycloalkyl or cycloalkenyl group having 3 to 7 ring members; the groups R^9 are the same or different and are each selected from hydrogen, C_{1-4} hydrocarbyl optionally interrupted by O, NR^c, S, SO or SO_2 and optionally substituted by a 5-7 membered carbocyclic or heterocyclic group, or two groups R^9 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic group; and R^{10} is hydrogen or C_{1-4} hydrocarbyl optionally interrupted by O, S, SO or SO_2 and optionally substituted by a 5-7 membered carbocyclic or heterocyclic group; R^2 is selected from aryl and heteroaryl having five to twelve ring members; cycloalkyl and cycloalkenyl having 3 to 7 ring members; a group $(CR^6R^7)_pE$-R^8 wherein p is 1 or 2, E is a bond, O, S or NR^9, R^6 and R^7 are the same or different and each is hydrogen, C_{1-4} alkyl or phenyl provided that the group (CR^6R^7)p contains no more than one phenyl group, and R^8 is C_{1-6} hydrocarbyl optionally interrupted by O, NR^c, S, SO or SO_2, a group R^4, phenyl or a mono- or bicyclic heterocyclic group having from five to ten ring members; or R^1 and R^2 together with the nitrogen atom to which they are attached form a heterocyclic group having 5 to 10 ring members; R^3 is a substituent selected from halogen, CN, N-linked monocyclic nitrogen-containing heterocyclic groups having from 3 to 7 ring members and containing up to three heteroatoms; and a group R^a-R^b wherein R^a is a bond, O, S, SO or SO^2; and R^b is NR^cR^d or C_{1-4} hydrocarbyl optionally interrupted by O, S, SO, SO_2, NR^c and optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino; and R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl.The compounds have activity as inhibitors of cyclin dependent kinases and are useful in the treatment of disease states and conditions, such as proliferative diseases, mediated by cyclin dependent kinases.

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PHARMACEUTICAL COMPOUNDS

This invention relates to 2,6-disubstituted pyrazine compounds that inhibit or modulate the activity of cyclin dependent kinases (CDK), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by cyclin dependent kinases, and to novel compounds having cyclin dependent kinase inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II,* Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.,* 9:576-596 (1995); Knighton, *et al., Science,* 253:407-414 (1991); Hiles, *et al., Cell,* 70:419-429 (1992); Kunz, *et al., Cell,* 73:585-596 (1993); Garcia-Bustos, *et al., EMBO J.,* 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These

phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system, and angiogenesis.

The process of eukaryotic cell division may be broadly divided into a series of sequential phases termed G1, S, G2 and M. Correct progression through the various phases of the cell cycle has been shown to be critically dependent upon the spatial and temporal regulation of a family of proteins known as cyclin dependent kinases (cdks) and a diverse set of their cognate protein partners termed cyclins. Cdks are cdc2 (also known as cdk1) homologous serine-threonine kinase proteins that are able to utilise ATP as a substrate in the phosphorylation of diverse polypeptides in a sequence dependent context. Cyclins are a family of proteins characterised by a homology region, containing approximately 100 amino acids, termed the "cyclin box" which is used in binding to, and defining selectivity for, specific cdk partner proteins.

Modulation of the expression levels, degradation rates, and activation levels of various cdks and cyclins throughout the cell cycle leads to the cyclical formation of a series of cdk/cyclin complexes, in which the cdks are enzymatically active. The formation of these complexes controls passage through discrete cell cycle checkpoints and thereby enables the process of cell division to continue. Failure to satisfy the pre-requisite biochemical criteria at a given cell cycle checkpoint, *i.e.*

failure to form a required cdk/cyclin complex, can lead to cell cycle arrest and/or cellular apoptosis. Aberrant cellular proliferation, as manifested in cancer, can often be attributed to loss of correct cell cycle control. Inhibition of cdk enzymatic activity therefore provides a means by which abnormally dividing cells can have their division arrested and/or be killed. The diversity of cdks, and cdk complexes, and their critical roles in mediating the cell cycle, provides a broad spectrum of potential therapeutic targets selected on the basis of a defined biochemical rationale.

Progression from the G1 phase to the S phase of the cell cycle is primarily regulated by cdk2, cdk3, cdk4 and cdk6 via association with members of the D and E type cyclins. The D-type cyclins appear instrumental in enabling passage beyond the G1 restriction point, where as the cdk2/cyclin E complex is key to the transition from the G1 to S phase. Subsequent progression through S phase and entry into G2 is thought to require the cdk2/cyclin A complex. Both mitosis, and the G2 to M phase transition which triggers it, are regulated by complexes of cdk1 and the A and B type cyclins.

During G1 phase Retinoblastoma protein (Rb), and related pocket proteins such as p130, are substrates for cdk(2, 4, & 6)/cyclin complexes. Progression through G1 is in part facilitated by hyperphosphorylation, and thus inactivation, of Rb and p130 by the cdk(4/6)/cyclin-D complexes. Hyperphosphorylation of Rb and p130 causes the release of transcription factors, such as E2F, and thus the expression of genes necessary for progression through G1 and for entry into S-phase, such as the gene for cyclin E. Expression of cyclin E facilitates formation of the cdk2/cyclin E complex which amplifies, or maintains, E2F levels via further phosphorylation of Rb. The cdk2/cyclin E complex also phosphorylates other proteins necessary for DNA replication, such as NPAT, which has been implicated in histone biosynthesis. G1 progression and the G1/S transition are also regulated via the mitogen stimulated Myc pathway, which feeds into the cdk2/cyclin E pathway. Cdk2 is also connected to the p53 mediated DNA damage response pathway via p53 regulation of p21 levels. p21 is a protein inhibitor of cdk2/cyclin E and is thus capable of

blocking, or delaying, the G1/S transition. The cdk2/cyclin E complex may thus represent a point at which biochemical stimuli from the Rb, Myc and p53 pathways are to some degree integrated. Cdk2 and/or the cdk2/cyclin E complex therefore represent good targets for therapeutics designed at arresting, or recovering control of, the cell cycle in aberrantly dividing cells.

The exact role of cdk3 in the cell cycle is not clear. As yet no cognate cyclin partner has been identified, but a dominant negative form of cdk3 delayed cells in G1, thereby suggesting that cdk3 has a role in regulating the G1/S transition.

Although most cdks have been implicated in regulation of the cell cycle there is evidence that certain members of the cdk family are involved in other biochemical processes. This is exemplified by cdk5 which is necessary for correct neuronal development and which has also been implicated in the phosphorylation of several neuronal proteins such as Tau, NUDE-1, synapsin1, DARPP32 and the Munc18/Syntaxin1A complex. Neuronal cdk5 is conventionally activated by binding to the p35/p39 proteins. Cdk5 activity can, however, be deregulated by the binding of p25, a truncated version of p35. Conversion of p35 to p25, and subsequent deregulation of cdk5 activity, can be induced by ischemia, excitotoxicity, and β-amyloid peptide. Consequently p25 has been implicated in the pathogenesis of neurodegenerative diseases, such as Alzheimer's, and is therefore of interest as a target for therapeutics directed against these diseases.

Cdk7 is a nuclear protein that has cdc2 CAK activity and binds to cyclin H. Cdk7 has been identified as component of the TFIIH transcriptional complex which has RNA polymerase II C-terminal domain (CTD) activity. This has been associated with the regulation of HIV-1 transcription via a Tat-mediated biochemical pathway. Cdk8 binds cyclin C and has been implicated in the phosphorylation of the CTD of RNA polymerase II. Similarly the cdk9/cyclin-T1 complex (P-TEFb complex) has been implicated in elongation control of RNA polymerase II. PTEF-b is also required for activation of transcription of the HIV-1 genome by the viral

transactivator Tat through its interaction with cyclin T1. Cdk7, cdk8, cdk9 and the P-TEFb complex are therefore potential targets for anti-viral therapeutics.

At a molecular level mediation of cdk/cyclin complex activity requires a series of stimulatory and inhibitory phosphorylation, or dephosphorylation, events. Cdk phosphorylation is performed by a group of cdk activating kinases (CAKs) and/or kinases such as wee1, Myt1 and Mik1. Dephosphorylation is performed by phosphatases such as cdc25(a & c), pp2a, or KAP.

Cdk/cyclin complex activity may be further regulated by two families of endogenous cellular proteinaceous inhibitors: the Kip/Cip family, or the INK family. The INK proteins specifically bind cdk4 and cdk6. $p16^{ink4}$ (also known as MTS1) is a potential tumour suppressor gene that is mutated, or deleted, in a large number of primary cancers. The Kip/Cip family contains proteins such as $p21^{Cip1,Waf1}$, $p27^{Kip1}$ and $p57^{kip2}$. As discussed previously p21 is induced by p53 and is able to inactivate the cdk2/cyclin(E/A) and cdk4/cyclin(D1/D2/D3) complexes. Atypically low levels of p27 expression have been observed in breast, colon and prostate cancers. Conversely over expression of cyclin E in solid tumours has been shown to correlate with poor patient prognosis. Over expression of cyclin D1 has been associated with oesophageal, breast, squamous, and non-small cell lung carcinomas.

The pivotal roles of cdks, and their associated proteins, in co-ordinating and driving the cell cycle in proliferating cells have been outlined above. Some of the biochemical pathways in which cdks play a key role have also been described. The development of monotherapies for the treatment of proliferative disorders, such as cancers, using therapeutics targeted generically at cdks, or at specific cdks, is therefore potentially highly desirable. Cdk inhibitors could conceivably also be used to treat other conditions such as viral infections, autoimmune diseases and neuro-degenerative diseases, amongst others. Cdk targeted therapeutics may also provide clinical benefits in the treatment of the previously described diseases when

used in combination therapy with either existing, or new, therapeutic agents. Cdk targeted anticancer therapies could potentially have advantages over many current antitumour agents as they would not directly interact with DNA and should therefore reduce the risk of secondary tumour development.

WO 02/34721 from Du Pont discloses a class of indeno [1,2-c]pyrazol-4-ones as inhibitors of cyclin dependent kinases.

WO 01/81348 from Bristol Myers Squibb describes the use of 5-thio-, sulfinyl- and sulfonylpyrazolo[3,4-b]-pyridines as cyclin dependent kinase inhibitors.

WO 00/62778 also from Bristol Myers Squibb disclose a class of protein tyrosine kinase inhibitors.

WO 01/72745A1 from Cyclacel describes 2-substituted 4-heteroaryl-pyrimidines and their preparation, pharmaceutical compositions containing them and their use as inhibitors of cyclin-dependant kinases (cdks) and hence their use in the treatment of proliferative disorders such as cancer, leukaemia, psoriasis and the like.

WO9921845A2 from Agouron describes 4-aminothiazole derivatives for inhibiting cyclin-dependent kinases(cdks), such as CDK1, CDK2, CDK4, and CDK6. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compositions containing such compounds and to methods of treating malignancies and other disorders by administering effective amounts of such compounds.

WO 00/76980 and WO 00/75113, both from Yamanouchi, describe various monocyclic heterocyclic compounds having a $CONH_2$ substituent group attached to the heterocyclic ring. The compounds are described as protein kinase C and Syk inhibitors respectively.

WO 01/85671 discloses a class of 1,2-disubstituted arylamine and heteroarylamine compounds as angiogenesis inhibitors.

WO 01/17995 from Merck describes various bis-heteroarylamine compounds as tyrosine kinase inhibitors.

WO 01/53274 from Agouron discloses as CDK kinase inhibitors a class of compounds which can comprise an amide-substituted benzene ring linked to an N-containing heterocyclic group.

WO 01/58899 from Novartis discloses further tyrosine kinase inhibitors. The general formula set out in this document encompasses pyridylaminopyrazines but no pyrazines are exemplified. The preferred and exemplified compounds are largely pyridines.

WO 01/85671 from Schering discloses compounds that are angiogenesis inhibitors (VEGF receptor binding). The compounds have a core aryl group that can be benzene, pyridine, pyrazine, pyrimidine or triazine group but must be 1,2-disubstituted.

WO 95/27699 from Nippon Shinyaku describes a class of aminostilbazoles that are considered to be useful in treating tumours.

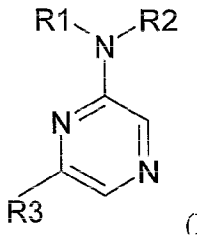
WO 99/32436 from the Bayer Corporation discloses a class of diaryl ureas as raf kinase inhibitors. The general formula disclosed in this document encompasses pyrazine but no pyrazines specifically mentioned or exemplified.

WO 99/46236 from Novo Nordisk and the Ontogen Corporation relates to a class of heterocyclic compounds that have tyrosine phosphotase inhibitory activity. Pyrazines are disclosed but there is no specific disclosure of 2,6-disubsituted pyrazines.

Summary of the Invention

The invention provides a novel class of compounds that have cyclin dependent kinase inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by the cyclin dependent kinases.

Accordingly, in a first aspect, the invention provides a compound of the general formula (I):



(I)

wherein R^1 is selected from hydrogen, cycloalkyl and cycloalkenyl having 3 to 7 ring members; phenyl-C_{1-4} alkyl or a group R^4-A-CH_2- wherein R^4 is selected from amino, mono- or di-C_{1-4} alkylamino, hydroxyl, C_{1-4} alkoxy, SH, $SO_2NR^9R^9$, $CONR^9R^9$, $NR^9SO_2R^{10}$ and NR^9COR^{10}, and A is a C_{1-4} alkylene chain or a group – $(CH_2)_m$-B-$(CH_2)_n$- wherein m and n are each independently 0, 1 or 2 and B is a divalent cycloalkyl or cycloalkenyl group having 3 to 7 ring members; the groups R^9 are the same or different and are each selected from hydrogen, C_{1-4} hydrocarbyl optionally interrupted by O, NR^c, S, SO or SO_2 and optionally substituted by a 5-7 membered carbocyclic or heterocyclic group, or two groups R^9 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic group; and R^{10} is hydrogen or C_{1-4} hydrocarbyl optionally interrupted by O, S, SO or SO_2 and optionally substituted by a 5-7 membered carbocyclic or heterocyclic group;

R^2 is selected from aryl and heteroaryl having five to twelve ring members; cycloalkyl and cycloalkenyl having 3 to 7 ring members; a group $(CR^6R^7)_p$-E-R^8 wherein p is 1 or 2, E is a bond, O, S or NR^9, R^6 and R^7 are the same or different and each is hydrogen, C_{1-4} alkyl or phenyl provided that the group $(CR^6R^7)_p$

contains no more than one phenyl group, and R^8 is C_{1-6} hydrocarbyl optionally interrupted by O, NR^c, S, SO or SO_2, a group R^4, phenyl or a mono- or bicyclic heterocyclic group having from five to ten ring members;

or R^1 and R^2 together with the nitrogen atom to which they are attached form a heterocyclic group having 5 to 10 ring members;

R^3 is a substituent selected from halogen; CN; N-linked monocyclic nitrogen-containing heterocyclic groups having from 3 to 7 ring members and containing up to three heteroatoms; and a group R^a-R^b wherein R^a is a bond, O, S, SO or SO_2, and R^b is NR^cR^d or C_{1-4} hydrocarbyl optionally interrupted by O, S, SO, SO_2, NR^c and optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino; and R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl.

R^1 can be selected from hydrogen, phenyl-C_{1-4} alkyl, cycloalkyl and cycloalkenyl having 3 to 7 ring members and a group R^4-A-CH_2-.

In one group of compounds of the invention, R^1 is hydrogen.

In another group of compounds of the invention, R^1 is selected from phenyl-C_{1-4} alkyl, cycloalkyl and cycloalkenyl groups having 3 to 7 ring members and a group R^4-A-CH_2-.

In one sub-group of compounds , R^1 is selected from phenyl-C_{1-4} alkyl and a group R^4-A-CH_2- as hereinbefore defined.

In a further sub-group of compounds, R^1 is selected from cycloalkyl and cycloalkenyl groups having 3 to 7 ring members.

Where R^1 is phenyl-C_{1-4} alkyl, preferably it is a phenylethyl or benzyl group, most preferably a benzyl group.

When R^1 is a group R^4-A-CH_2-, the group A can be a C_{1-4} alkylene chain or a group $-(CH_2)_m$-B-$(CH_2)_n$-. Where the group A is an alkylene chain, preferably it is one, two or three carbon atoms in length, more preferably two or three carbon atoms in

length, and in particular it may be selected from any one or more of methylene, ethylene and propylene.

When the group A is $-(CH_2)_m$-B-$(CH_2)_n$-, m and n are preferably both 0. Typically, B is a divalent cycloalkyl or cycloalkenyl group (preferably a cycloalkyl group) having 5 to 7 ring members and most preferably cyclohexyl.

R^4 can be for example an amino or hydroxyl group, or a group selected from $SO_2NR^9R^9$ (e.g. SO_2NH_2), $CONR^9R^9$, $NR^9SO_2R^{10}$ and NR^9COR^{10}, preferably an amino, or hydroxyl group.

In one preferred group of compounds, R^4 can be an amino or hydroxyl group.

Where R^9 is C_{1-4} hydrocarbyl, it can be, for example, a methyl or ethyl group.

Where two groups R^9 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic group, the heterocyclic group can be for example selected from morpholine, piperidine, piperazine, and pyrrolidine.

Alternatively, R^9 can be hydrogen.

Particular examples of the group R^4-A-CH_2- are 3-aminopropyl, 2-hydroxyethyl, 3-hydroxypropyl and 2-hydroxycyclohexylmethyl.

One preferred group of compounds of the invention is the group of compounds wherein R^1 is selected from phenyl-C_{1-4} alkyl or a group R^4-A-CH_2-, and R^2 is a cycloalkyl or cycloalkenyl group having 3 to 7 ring members.

R^2 can be an aryl or heteroaryl group. The terms "aryl" and "heteroaryl" as used herein, except where the context indicates otherwise, refer to a carbocyclic or heterocyclic group having aromatic character. The aryl or heteroaryl group can be a monocyclic or bicyclic group and can be unsubstituted or substituted with one or more substituents. Where reference is made to a specific type of aryl or heteroaryl

group such as a phenyl, pyrazolyl, isoxazolyl or pyridyl group etc, such references are intended to refer to both unsubstituted and substituted groups, unless the context indicates otherwise. Thus, for example, the term "phenyl" includes both unsubstituted and substituted phenyl groups.

The terms "aryl" and "heteroaryl" as used herein embraces polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. Where one ring in a polycyclic ring system is non-aromatic, the point of attachment is to the aromatic part of the polycyclic ring system.

Where the group R^2 is a heteroaryl group, it is selected from monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Monocyclic rings are currently preferred. Each ring may contain up to about four heteroatoms, more usually three or fewer, and typically one, two or three. The heteroatoms are typically selected from nitrogen, sulphur and oxygen. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of heteroaryl groups R^2 include but are not limited to pyridyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, triazinyl, triazolyl, quinolinyl, isoquinolinyl, tetrazolyl, benzfuranyl, benzthienyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl,

purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

In one sub-group of compounds of the formula (I), R^1 is hydrogen and R^2 is a phenyl group or a heteroaryl group as hereinbefore defined.

Where R^2 is a heteroaryl group, it is preferably a five or six membered heteroaryl group having five or six ring members. In one embodiment, the heteroaryl group has one or two heteroatoms which can be selected from nitrogen, oxygen and sulphur.

In one particular sub-group of compounds R^2 is a monocyclic heteroaryl group containing one heteroatom ring member.

In another sub-group, R^2 is a monocyclic heteroaryl group having five ring members, 1 or 2 of which are heteroatoms selected from nitrogen, oxygen and sulphur, but excluding oxazole, thiazole and imidazole.

Preferred heteroaryl groups are pyridyl (e.g. 2-pyridyl and 3-pyridyl), thienyl and pyrazolyl.

In one embodiment of the invention, R^2 is other than unsubstituted 2-pyrimidinyl and 3,4-disubstituted 5-thiazolyl.

The aryl and heteroaryl groups R^2 can be unsubstituted or substituted by one or more substituent groups R^{11}. Examples of substituent groups include but are not limited to halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic or bicyclic carbocyclic or heterocyclic groups having from 3 to 10 ring members (preferably 3 to 7) and containing up to three heteroatoms; a group R^a-R^b

wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c, NR^cSO_2; R^b is hydrogen, C_{1-8} hydrocarbyl optionally interrupted by O, S, SO, SO_2, NR^c, CO, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; the monocyclic or bicyclic C_{3-10} carbocyclic or heterocyclic groups and R^b being optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, monocyclic carbocyclic or heterocyclic groups having from 3 to 7 ring members and containing up to three heteroatoms; R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl; X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

Where the substituent group R^{11} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups. In one sub-group of compounds of the formula (I), such further substituent groups R^{11} may include carbocyclic or heterocyclic groups. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{10}.

In one general embodiment, the substituent groups R^{11} may be selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

In another general embodiment, the group R^b may be a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined, and wherein one or more carbon atoms thereof may be optionally replaced as hereinbefore defined.

Examples of halogen substituents include fluorine, chlorine and bromine, fluorine and chlorine (and most preferably chlorine) being particularly preferred.

In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms. Examples of such groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

Generally by way of example, the hydrocarbyl groups can have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} hydrocarbyl groups, such as C_{1-4} hydrocarbyl groups (e.g. C_{1-3} hydrocarbyl groups or C_{1-2} hydrocarbyl groups), specific examples being any individual value or combination of values selected from C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 hydrocarbyl groups.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include C_{1-8} alkyl groups, such as C_{1-6} alkyl groups (e.g. C_{1-4} alkyl groups or C_{1-3} alkyl groups), particular examples being methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers.

Examples of cycloalkyl groups are C_{3-7} cycloalkyl groups, more particularly C_{3-6} cycloalkyl groups, with particular examples being those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane.

Examples of alkenyl groups include, but are not limited to, C_{2-8} alkenyl groups, such as C_{2-6} alkenyl groups (e.g. C_{2-4} alkenyl groups or C_{2-3} alkenyl groups), particular examples being ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl,

Examples of cycloalkenyl groups include, but are not limited to, C_{3-7} cycloalkenyl groups, more particularly C_{3-6} cycloalkenyl groups, with particular examples being cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl.

Examples of alkynyl groups include, but are not limited to, C_{2-8} alkynyl groups, such as C_{2-6} alkynyl groups (e.g. C_{2-4} alkynyl groups or C_{2-3} alkynyl groups), particular examples being ethynyl and 2-propynyl (propargyl) groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups are those in which the carbon number ranges and specific examples of the cycloalkyl, cycloalkenyl and carbocyclic aryl residues and the alkyl, alkenyl and alkynyl residues are as hereinbefore defined. Particular examples of such groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

Where stated, one or more carbon atoms of a hydrocarbyl group (e.g. a C_{1-8} , C_{1-6} or C_{1-4} hydrocarbyl group) may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ wherein X^1 and X^2 are as hereinbefore defined. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced

by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. Examples of groups in which a carbon atom of the hydrocarbyl group has been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2) and amines (C replaced by NR^c).

As defined above, the aryl (e.g. phenyl) or heteroaryl group R^2 can be unsubstituted or substituted with one or more substituents. Preferably, when substituted, the group R^2 bears one or two substituents, more preferably a single substituent group. Examples of substituents are OH, halogen, C_{1-4} alkyl, $SO_2NR^eR^f$, CO_2H, $CO_2NR^eR^f$, CO_2R^e, NR^cR^g wherein R^e and R^f are each hydrogen or C_{1-4} alkyl groups and R^g is a group R^e or a C_{1-4} alkanoyl group.

Particular substituents are OH, SO_2NH_2, fluorine, chlorine, methyl, carbamoyl, carboxy and acetamido.

R^2 can be selected from cycloalkyl and cycloalkenyl groups having 3 to 7 ring members (more typically 5 or 6 ring members), and is preferably a cycloalkyl group. Examples of cycloalkyl and cycloalkenyl groups are set forth above in the definition of "hydrocarbyl". Particular examples of cycloalkyl groups are cyclopentyl, cyclohexyl and cycloheptyl, with cyclopentyl and particularly cyclohexyl being most preferred.

It is preferred that when R^2 is a cyclohexyl group, it is unsubstituted or is substituted at the 3- or 4- positions, or is substituted at the 2-position by a substituent other than an amino or hydroxyl group.

In another sub-group of compounds of the formula (I), R^2 is a group $(CR^6R^7)_p$-E-R^8 wherein p, E, R^6, R^7 and R^8 are as hereinbefore defined. Within this sub-group of compounds are the compounds in which (i) E is a bond; or (ii) E is O, S or NR^9 ; or (iii) E is NR^9; and wherein preferably R^8 is phenyl or a mono- or bicyclic

heterocyclic group having from five to ten ring members; provided that R^2 is other than an unsubstituted benzyl group, a 4-aminosulphonylbenzyl group or a 2-acetamido-thiazol-4-ylmethyl group.

The groups R^6 and R^7 are typically, but not exclusively, are each hydrogen or phenyl provided that no more than one phenyl group is present. Examples of the group $(CR^6R^7)_p$ include CH_2, CH_2CH_2 and CHPh where Ph is a phenyl group.

The group R^8 is C_{1-6} hydrocarbyl optionally interrupted by O, NR^c, S, SO or SO_2, a group R^4, phenyl or a mono- or bicyclic heterocyclic group having from five to ten ring members. The mono- or bicyclic heterocyclic group can be a heteroaryl group or a partially or fully saturated group.

Where R^8 is a phenyl group or a mono- or bicyclic heterocyclic group (e.g. heteroaryl group), it can be a group as defined above in relation to R^2, the particular examples, preferences, and optional substituent groups set out above for R^2 also applying to R^8. Within this context, particular examples of heteroaryl groups are indole (e.g. indol-5-yl), furyl (e.g. 2-furyl), isoxazolyl (e.g. 5-isoxazolyl), thienyl (e.g. 2-thienyl), pyrazinyl and imidazolyl (e.g. 4-(1H) imidazolyl) groups.

Where R^8 is a non-aromatic heterocyclic group, it can be a mono- or bicyclic heterocyclic group which is partially or fully saturated. For example, R^8 can be a ring containing up to three heteroatoms selected from nitrogen, sulphur and oxygen. Typically at least one nitrogen atom will be present. Particular examples of such groups include piperidine, piperazine, N-methylpiperazine, morpholine, pyrrolidine, imidazoline, imidazolidine, thiazoline, thiazolidine, oxazoline, oxazolidine and tetrahydrofuran. Preferred non-aromatic heterocyclic groups include pyrrolidine. The mono- or bicyclic heterocyclic group can be a heteroaryl group or a non-aromatic heterocyclic group as hereinbefore defined.

Where R^8 is a C_{1-6} hydrocarbyl group optionally interrupted by O, NR^c, S, SO or SO_2, preferably it contains 2 to 6 carbon atoms, more preferably 3 to 6. For example, the group can be a branched chain C_{3-6} alkyl group.

It is preferred that when $(CR^6R^7)_p$-E-R^8 constitutes a benzyl group, the benzyl group is substituted by one or more substituents other than a 4-aminosulphonyl group, and that when $(CR^6R^7)_p$-E-R^8 constitutes a thiazol-4-ylmethyl group, the thiazolyl ring is unsubstituted or substituted with a substituent other than 2-acetamido.

In another group of compounds of the formula (I), R^1 and R^2 together with the nitrogen atom to which they are attached form a heterocyclic group having 5 to 10 ring members. The heterocyclic group can be monocyclic or bicyclic and can be for example selected from 5-membered monocyclic, 6-membered monocyclic, 5.6-fused bicyclic and 6.6-fused bicyclic groups.

The heterocyclic group can be aromatic, partially saturated or fully saturated. Aryl or heteroaryl rings within the heterocyclic group can be unsubstituted or substituted by one or more substituent groups as defined above in relation to aryl and heteroaryl groups of the group R^2.

In one embodiment, the heterocyclic group can be a benzo-fused heterocycle such as quinoline, isoquinoline, indole or benzimidazole and forms thereof in which the heterocyclic ring is partially or fully reduced.

In another embodiment, the heterocyclic group is a heteroaryl group.

Examples of preferred heterocyclic groups include tetrahydroisoquinolinyl, benzimidazolyl, benzimidazolone, piperazine, imidazole, pyrrole and pyrazole.

R^3 is a substituent selected from halogen; CN, N-linked monocyclic nitrogen-containing heterocyclic groups having from 3 to 7 ring members and containing up

to three heteroatoms; and a group R^a-R^b wherein R^a is a bond, O, S, SO or SO_2; and R^b is NR^cR^d, a group R^e, or C_{1-4} hydrocarbyl optionally interrupted by O, S, SO, SO_2, NR^c and optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino or a group R^e; R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl; and R^e is C_{3-7} cycloalkyl or cycloalkenyl, phenyl or a monocylic nitrogen-containing heterocyclic group having from 3 to 7 ring members.

It is preferred that R^3 is other than a 5-methylpyrazolyl or N-pyrrolidonyl group

Preferably R^3 is a halogen (particularly chlorine, bromine or fluorine, and most preferably chlorine), a fluorinated C_{1-4} alkoxy group such as trifluoroethoxy, a C_{1-4} alkylsulfanyl group such as methylthio, or a small heterocyclic ring, for example a five membered nitrogen heterocycle containing 1 or 2 nitrogen atom ring members. Typically the five membered heterocycle is other than an N-pyrrolidone or N-pyrazolyl group, and preferably the five membered heterocycle is an imidazolyl group linked to the pyrazine ring through a nitrogen atom.

For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example of the groups R^1 may be combined with each general and specific preference, embodiment and example of the groups R^2 and/or R^3 and that all such combinations are embraced by this application.

The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

Particular compounds of the invention are:

2-chloro-6-cyclopentylaminopyrazine;

(6-chloro-pyrazin-2-yl)-phenyl-amine;

6-(3-aminosulphonylphenylamino)-2-chloropyrazine;

5-(2-chloropyrazin-6-ylaminomethyl)-2-methylindole;

2-chloro-6-(2-chlorothiophen-5-ylmethylamino)pyrazine;

N-1-(6-chloro-pyrazin-2-yl)-N-1-cyclohexyl-propane-1,3-diamine;

(6-chloro-pyrazin-2-yl)-pyrrolidin-2-ylmethyl-amine;

3-(6-chloro-pyrazin-2-ylamino)-phenol;

3-(6-chloro-pyrazin-2-ylamino)-thiophene-2-carboxylic acid amide;

4-(6-chloro-pyrazin-2-ylamino)-benzenesulfonamide;

2-{[(6-chloro-pyrazin-2-yl)-cyclohexyl-amino]-methyl}-cyclohexanol;

N-[4-(6-chloro-pyrazin-2-ylamino)-phenyl]-acetamide;

benzhydryl-(6-chloro-pyrazin-2-yl)-amine;

(6-chloro-pyrazin-2-yl)-pyridin-3-yl-amine;

(6-chloro-pyrazin-2-yl)-cyclohexyl-amine;

4-(6-chloro-pyrazin-2-ylamino)-phenol;

5-[(6-chloro-pyrazin-2-ylamino)-methyl]-furan-2-carboxylic acid ethyl ester;

(6-chloro-pyrazin-2-yl)-[3-(6-chloro-pyrazin-2-yloxy)-isoxazol-5-ylmethyl]-amine;

N,N'-bis-(6-chloro-pyrazin-2-yl)-ethane-1,2-diamine;

(6-chloro-pyrazin-2-yl)-(5-methyl-2H-pyrazol-3-yl)-amine;

2-[(6-chloro-pyrazin-2-yl)-cyclohexyl-amino]-ethanol;

2-(6-chloro-pyrazin-2-ylamino)-ethanesulfonic acid amide;

benzyl-(6-chloro-pyrazin-2-yl)-cyclohexyl-amine;

(6-chloro-pyrazin-2-yl)-[2-(1H-imidazol-4-yl)-ethyl]-amine;

2-(6-chloro-pyrazin-2-yl)-1,2,3,4-tetrahydro-isoquinoline;

6'-chloro-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl;

(6-chloro-pyrazin-2-yl)-isobutyl-amine;

(6-chloro-pyrazin-2-yl)-(4-fluoro-phenyl)-amine;

1-(6-chloro-pyrazin-2-yl)-1,3-dihydro-benzoimidazol-2-one;

2-chloro-6-pyrazol-1-yl-pyrazine;

(6-chloro-pyrazin-2-yl)-pyridin-2-yl-amine;

(6-chloro-pyrazin-2-yl)-(5-chloro-pyridin-2-yl)-amine;

1-(6-chloro-pyrazin-2-yl)-1H-benzoimidazole;

6-(6-chloro-pyrazin-2-ylamino)-nicotinic acid;
5-tert-butyl-2-(6-chloro-pyrazin-2-yl)-2H-pyrazol-3-ylamine;
phenyl-[6-(2,2,2-trifluoroethoxy)-pyrazin-2-yl]-amine;
(6-methylsulfanyl-pyrazin-2-yl)-phenyl-amine;
[6-(2-isopropyl-imidazol-1-yl)-pyrazin-2-yl]-phenyl-amine;
2-(1-imidazolyl)-6-phenylaminopyrazine; and
2,6-bis(1-imidazolyl)pyrazine.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

Compounds of the formula may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any

compound that is converted *in vivo* into a biologically active compound of the formula (I).

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). Examples of esters are compounds containing the group -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh. Examples of acyloxy (reverse ester) groups are represented by -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

Where the compounds of the formula (I) contain chiral centres, all individual optical forms such as enantiomers, epimers and diastereoisomers, as well as racemic mixtures of the compounds are within the scope of formula (I).

The compounds of the formula (I) are inhibitors of cyclin dependent kinases. As such, they are expected to be useful in providing a means of arresting, or recovering control of, the cell cycle in abnormally dividing cells. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. It is also envisaged that the compounds of the invention will be useful in treating conditions such as viral infections, autoimmune diseases and neurodegenerative diseases for example.

CDKs play a role in the regulation of the cell cycle, apoptosis, transcription, differentiation and CNS function. Therefore, CDK inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or

differentiation such as cancer. In particular RB+ve tumours may be particularly sensitive to CDK inhibitors.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas, such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acutelymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins' lymphoma, non-Hodgkins' lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma, ; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

CDKs are also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore CDK inhibitors could also be useful in the treatment of the following diseases other than cancer; viral infections, for example herpes virus, poxvirus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and

cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-senstive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

It has also been discovered that some cyclin-dependent kinase inhibitors can be used in combination with other anticancer agents. For example, the cytotoxic activity of cyclin-dependent kinase inhibitor flavopiridol, has been used with other anticancer agents in combination therapy.

Accordingly, in another aspect, the invention provides a compound of the formula (I) as hereinbefore defined for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, for example a disease state or condition as set out above.

The invention also provides the use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

In a further aspect, the invention provides a method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

This invention also provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of formula (I) in an amount effective in inhibiting abnormal cell growth.

This invention also provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of formula (I) in an amount effective to inhibit cdk2 activity.

Thus, in the pharmaceutical compositions or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer, non-small cell lung carcinomas.

The invention also provides a method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.

The invention further provides a method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound of the formula (I) as defined herein.

In a further aspect, the invention provides a pharmaceutical composition comprising a compound of the formula (I) as hereinbefore defined and a pharmaceutically acceptable carrier.

The invention also provides a compound of the formula (I) for use in medicine.

Methods for the Preparation of Compounds of the Formula (I)

The compounds of the formula (I) may be prepared using methods known in the art or analogous thereto, modified as necessary to suit the properties of the particular functional groups present in the compounds.

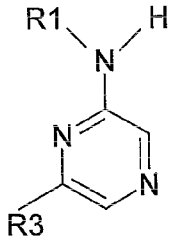
By way of example, compounds of the formula (I) can be prepared using 2,6-dichloropyrazine as a starting material. For example, 2,6-dichloropyrazine can be reacted with an amine suitable for introducing the group NR^1R^2 in a polar aprotic solvent such as tetrahydrofuran in the presence of a base, for example an amine such as triethylamine or N-methylpyrrolidine (NMP), or a metal hydride such as sodium hydride, to give a compound of the formula (I) wherein R^3 is chlorine.

Compounds wherein R^3 is a substituent group other than chlorine can readily be prepared from compounds of the formula (I) wherein R^3 is chlorine by further reaction with a reagent or reagent suitable for introducing such other substituent groups. For example, compounds wherein R^3 is an alkoxy group such as trifluoroethoxy (e.g. 2,2,2-trifluoroethoxy) can be prepared by reacting the relevant alkoxide with the chloropyrazine. The alkoxide can be generated *in situ* from the corresponding alcohol (e.g. trifluoroethanol) using a suitably strong base such as a metal hydride, e.g. sodium hydride. The reaction is typically carried out in a polar aprotic solvent such as dimethylsulphoxide.

Analogous processes can be used to introduce other substituents such as alkylsulfanyl groups. Thus, for example, the appropriate mercaptan (e.g. CH_3SH) can be treated with a strong base such as sodium hydride in a solvent such as DMSO and then reacted with the 6-chloropyrazine.

Heterocyclic substituents such as imidazole, bearing at least one labile N-H moiety can similarly be reacted with sodium hydride to generate a sodium salt of the anion which is then reacted with the 6-chloropyrazine.

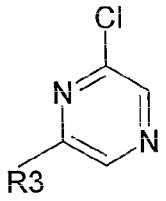
Compounds of the formula (I) can also be prepared by reacting a compound of the formula (II):



(II)

with a compound of the formula R^2-L where L is a suitable leaving group such as halogen. Alkylations of this type can be carried out in a polar aprotic solvent such as THF in the presence of a base such as a metal hydride.

Compounds of the formula (II) can be prepared from the corresponding compound of the formula (III):



(III)

by reaction with the appropriate amine under the conditions described above.

Compounds of the formula (I) can also be prepared from other compounds of the formula (I) by functional group interconversions well known to those skilled in the art, see for example, *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2), and *Organic Syntheses*, Volumes 1-8, John Wiley, edited by Jeremiah P. Freeman (ISBN: 0-471-31192-8), 1995.

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc). An aldehyde or ketone group may be protected, for example, as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid. An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as a sulphonamide such as a methane sulphonyl (mesyl) amide or a toluene sulphonyl (tosyl) amide, as an allyloxy amide (-NH-Alloc), or as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec). A carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide. A thiol group may be protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

A more detailed description of the processes that can be used to prepare the compounds of the formula (I) can be found in the specific examples set out below.

Pharmaceutical Formulations

The invention also provides compounds of the formula (I) as hereinbefore defined in the form of pharmaceutical compositions.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered

formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams.
The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

Methods of Treatment

It is envisaged that the compounds of the formula (I) will useful in the prophylaxis or treatment of a range of disease states or conditions mediated by cyclin dependent kinases. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human. The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include cytotoxic agents, agents that prevent cell proliferation or radiotherapy. Examples of such agents include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders and microtubule inhibitors, such as cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes and mitomycin C.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

In the examples, the compounds prepared were characterised by liquid chromatography and mass spectroscopy using two systems, the details of which are set out below. Where chlorine is present mass quoted for the compound is for ^{35}Cl. The two systems were equipped with identical chromatography columns and were set up to run under the same operating conditions. The operating conditions used are also described below.

1. Platform system

System:	Waters 2790/Platform LC
Mass Spec Detector:	Micromass Platform LC
PDA Detector:	Waters 996 PDA

Analytical conditions:

Eluent A:	H_2O (1% Formic Acid)
Eluent B:	CH_3CN (1% Formic Acid)
Gradient:	5-95% eluent B

Flow: 1.5 ml/min

Column: Synergi 4μm Max-RP C_{12}, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage: 3.5 kV

Cone voltage: 30 V

Source Temperature: 120 °C

2. FractionLynx system

System: Waters FractionLynx (dual analytical/prep)

Mass Spec Detector: Waters-Micromass ZQ

PDA Detector: Waters 2996 PDA

Analytical conditions:

Eluent A: H_2O (1% Formic Acid)

Eluent B: CH_3CN (1% Formic Acid)

Gradient: 5-95% eluent B

Flow: 1.5 ml/min

Column: Synergi 4μm Max-RP C_{12}, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage: 3.5 kV

Cone voltage: 30 V

Source Temperature: 120 °C

Desolvation Temperature: 230 °C

The starting materials for each of the Examples are commercially available unless otherwise specified.

EXAMPLE 1

General Synthetic Procedure A

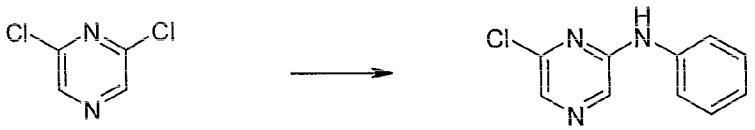
Synthesis of 2-Chloro-6-cyclopentylaminopyrazine

To a stirred solution of the 2,6-dichloropyrazine (100 mg, 0.67 mmol) in tetrahydrofuran (THF) (2.0 ml) was added cyclopentylamine (60 mg, 0.87 mmol) and triethylamine (121 ul, 0.87 mmol). The reaction was warmed to 50 °C for 1 day. The reaction mixture was allowed to cool to room temperature, quenched with water, and then partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash chromatography on silica (by gradient elution from 100% dichloromethane to 100% ethyl acetate) to afford the title compound; LCMS: m/z 198.2 (M+H), RT 4.30 min.

EXAMPLE 2

General Synthetic Procedure B

Preparation of (6-Chloro-pyrazin-2-yl)-phenyl-amine

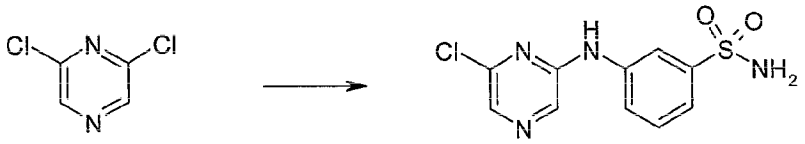


To a solution of 2,6-dichloropyrazine (5 g, 33.5 mmol, 1.0 equiv) in *N*-methylpyrrolidine (NMP) (11 ml) was added aniline (3.4 ml, 36.9 mmol, 1.1 equiv). The mixture was then heated to 190°C under microwave assisted heating (50 to 200 watts) for 20 minutes at atmospheric pressure. The reaction was cooled to room temperature and water (10 ml) and 1N NaOH (10 ml) were added. The mixture was extracted three times with diethyl ether. The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The title compound was purified by flash chromatography on silica (100 g, SiO_2) eluted with 15% ethyl acetate-petrol to afford 3.1 g (45%); LCMS 3.74 min, *m/z* $[M(^{35}Cl)+H]^+$ 206.

EXAMPLE 3

General Synthetic Procedure C

Preparation of 6-(3-Aminosulphonylphenylamino)-2-chloropyrazine

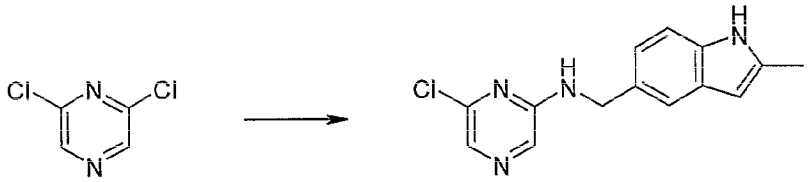


To a solution of the 2,6-dichloropyrazine (100 mg, 0.67 mmol) in NMP (2 ml) was added 3-aminobenzenesulfonamide (150 ml, 0.87 mmol). The reaction was heated to 250 °C under microwave assisted heating for 5 minutes. The reaction mixture was cooled, quenched with Na_2CO_3 (saturated, aq.), and then partitioned between ethyl acetate and water. The organic layer was separated and washed with water, then brine, and dried over $MgSO_4$. The product was filtered and evaporated to dryness. The crude product was purified by flash chromatography on silica (by gradient elution from 10% ethyl acetate/petrol to 100% ethyl acetate) to afford the title compound; LCMS: m/z 285 (M+H), RT 3.21 min.

EXAMPLE 4

General Synthetic Procedure D

Preparation of 5-(2-Chloropyrazin-6-ylaminomethyl)-2-methylindole



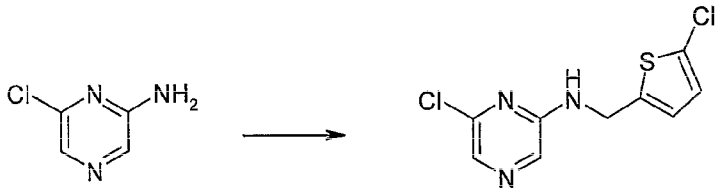
To a solution of the 2,6-dichloropyrazine (150 mg, 1.01 mmol) in NMP (2 ml) was added *C*-(2-methyl-1H-indol-5-yl)-methylamine (178 ml, 1.11 mmol). The reaction was heated to 100 °C for 2 days. The reaction mixture was cooled, quenched with Na_2CO_3 (aq.), and then partitioned between ethyl acetate and water. The organic layer was separated and washed with water, then brine, and dried over $MgSO_4$. The product was filtered and evaporated to dryness. The crude product was purified by flash chromatography on silica (by gradient elution from 10% ethyl acetate/petrol to

100% ethyl acetate) to afford the title compound; LCMS: m/z 273 (M+H), RT 3.80 min.

EXAMPLE 5

General Synthetic Procedure E

Preparation of 2-Chloro-6-(2-chlorothiophen-5-ylmethylamino)pyrazine

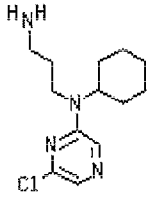
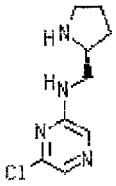
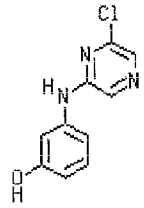
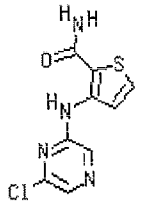
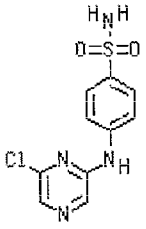


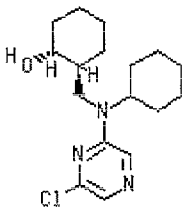
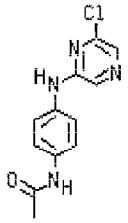
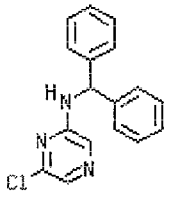
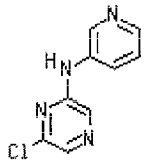
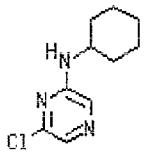
To a stirred solution of the 2-amino-6-chloropyrazine (149 mg, 1.15 mmol) in THF (2 ml) was added Bu_4NI (5 mg, cat.) and then the NaH (56 mg, 1.39 mmol) at room temperature under an atmosphere of nitrogen. After 10 minutes, 2-chloro-5-(chloromethyl)thiophene (138 mg, 1.15 mmol) was added. The reaction was left for 3 hours at room temperature, quenched with water, and then partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash chromatography on silica (eluent 20% ethyl acetate/ petrol) to afford the title compound; LCMS: m/z 260 (M+H), RT 4.13 min.

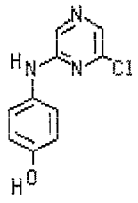
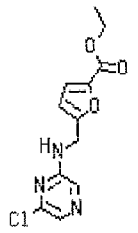
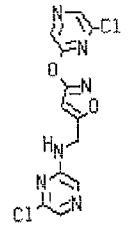
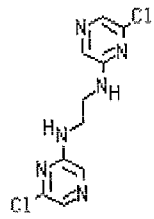
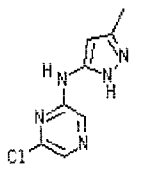
EXAMPLES 6- 27

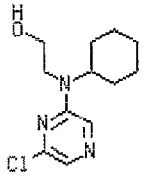
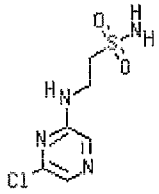
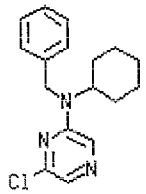
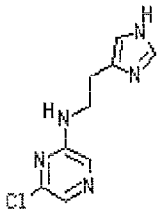
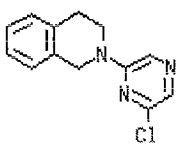
By following the general synthetic procedures A-E set out in Examples 1 to 5, and using the appropriate amine or chloromethyl compound, the compounds listed in Table 1 were prepared.

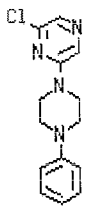
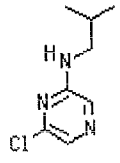
Table 1

Example No.	Synthetic Procedure	Structure	Average Molecular Weight	LC Retention time	LCMS m/z (M+1)
6	A		268.8	2.22	MH^+ 269
7	A		212.7	1.74	MH^+ 213
8	C		221.6	3.44	MH^+ 222
9	B		254.7	3.20	MH^+ 255
10	C		284.7	2.74	MH^+ 285

Example No.	Synthetic Procedure	Structure	Average Molecular Weight	LC Retention time	LCMS m/z (M+1)
11	A		322.9	5.22	MH^+ 324
12	C		262.7	2.77	MH^+ 263
13	D		295.8	4.41	MH^+ 296
14	B		206.6	1.93	MH^+ 207
15	B		211.7	4.60	MH^+ 212

Example No.	Synthetic Procedure	Structure	Average Molecular Weight	LC Retention time	LCMS m/z (M+1)
16	C		221.6	2.90	MH^+ 222
17	E		281.7	3.59	MH^+ 282
18	A		339.1	3.56	MH^+ 339
19	A		285.1	3.52	MH^+ 285
20	B		209.6	3.30	MH^+ 210

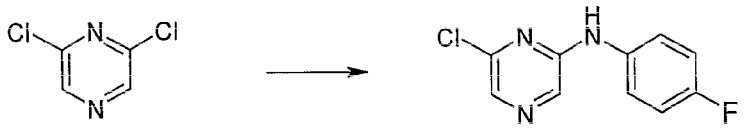
Example No.	Synthetic Procedure	Structure	Average Molecular Weight	LC Retention time	LCMS m/z (M+1)
21	A		255.7	4.15	MH^+ 256
22	A		236.7	2.46	MH^+ 237
23	E		301.8	5.64	302
24	A		223.7	0.43	MH^+ 224
25	A		245.7	4.80	246

Example No.	Synthetic Procedure	Structure	Average Molecular Weight	LC Retention time	LCMS m/z (M+1)
26	B		274.7	4.67	MH^+ 275
27	B		185.7	4.23	MH^+ 186

EXAMPLE 28

General Synthetic Procedure F

Preparation of (6-Chloro-pyrazin-2-yl)-(4-fluoro-phenyl)-amine

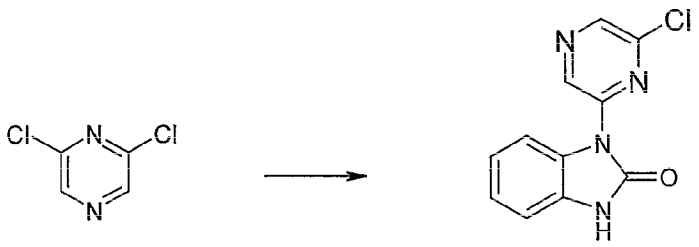


A mixture of 4-fluoroaniline (0.129 ml, 1.34 mmol) and 2,6-dichloropyrazine (0.2 g, 1.34 mmol, 1 eq.) in NMP (10 ml) was heated to 190 °C for 54 hours. The product was purified by column chromatography to yield the product. LCMS 3.81 min, *m/z* $[M+H]^+$ 224.

EXAMPLE 29

General Synthetic Procedure G

Preparation of 1-(6-Chloro-pyrazin-2-yl)-1,3-dihydro-benzoimidazol-2-one

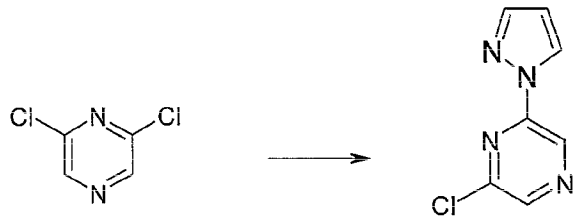


To a mixture of 2-hydroxybenzimidazole (0.18 ml, 1.34 mmol) and 2,6-dichloropyrazine (0.2 g, 1.34 mmol, 1 eq.) in THF (10 ml) was added NaH (54 mg, 60% in mineral oil). The reaction mixture was heated to 80 °C for 18 hours. The reaction mixture was allowed to cool and quenched by pouring into $NaHCO_3$ (aq., sat.) and extracting the product with EtOAc (x2). The combined organic layers were washed with brine and dried over $MgSO_4$. The product was filtered, evaporated to dryness and purified by column chromatography to yield the product. LCMS 3.22 min, *m/z* $[M+H]^+$ 247.

EXAMPLE 30

General Synthetic Procedure H

Preparation of 2-Chloro-6-pyrazol-1-yl-pyrazine



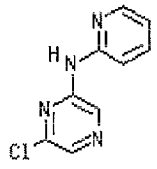
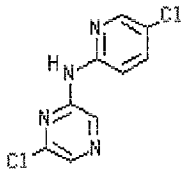
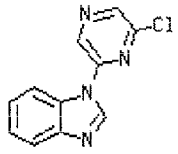
To NaH (0.15 mg, 3.70 mmol, 1.1 eq.) in DMSO (1.5 ml) was added the pyrazole (0.23 ml, 3.36 mmol) in DMSO (1.5 ml) and the reaction mixture was stirred for 30 minutes. 2,6-dichloropyrazine (0.5 g, 3.36 mmol, 1 eq.) was then added and the reaction was allowed to stir at room temperature for 30 minutes before being heated to 100 °C for 5 hours. The reaction was quenched with water and the product extracted with EtOAc (x2). The combined organic layers were washed again with water, then brine and dried over $MgSO_4$. The product was filtered, evaporated to

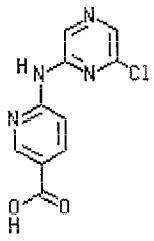
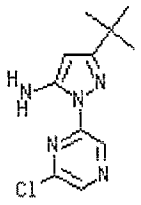
dryness and purified by column chromatography to yield the product. LCMS 3.20 min, *m/z* $[M+H]^+$ 181.

EXAMPLES 31- 34

By following the general synthetic procedure H set out in Example 30, and using the appropriate amine, the compounds listed in Table 2 were prepared.

Table 2

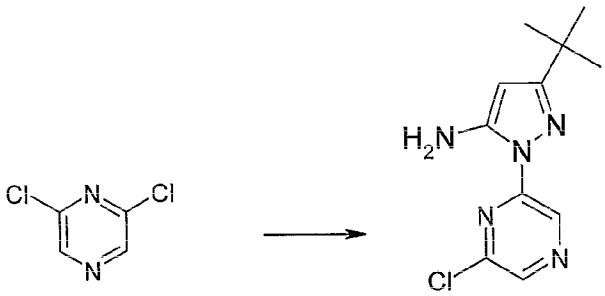
Example No.	Synthetic Procedure	Structure	Average Molecular Weight	LC Retention time	LCMS m/z (M+1)
31	H		206.7	2.03	207
32	H		241.1	3.86	MH^+ 242
33	H		230.7	3.27	MH^+ 231

Example No.	Synthetic Procedure	Structure	Average Molecular Weight	LC Retention time	LCMS m/z (M+1)
34	H		250.7	2.64	MH^+ 251
35	H		251.8	4.57	252

EXAMPLE 35

General Synthetic Procedure I

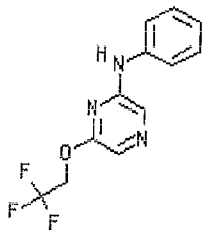
Preparation of 5-tert-Butyl-2-(6-chloro-pyrazin-2-yl)-2H-pyrazol-3-ylamine



A mixture of 2-chloro-6-hydrazinopyrazine (65 mg, 0.45 mmol) and pivaloylacetonitrile (57, 0.45 mmol, 1 eq) in EtOH (2 ml) were refluxed for 16 hours. The reaction was evaporated to dryness in vacuo and partitioned between water and EtOAc. The organic layer was separated and dried with brine and then over $MgSO_4$. The product was filtered, evaporated to dryness and purified by column chromatography to yield the product. LCMS 4.57 min, *m/z* $[M+H]^+$ 252.

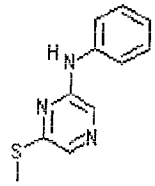
EXAMPLE 36

36A. Preparation of Phenyl-[6-(2,2,2-trifluoroethoxy)-pyrazin-2-yl]-amine



To sodium hydride (50 mg, 1.25 mmol of a 60% dispersion in oil, 1.5 equiv) in DMSO (1 ml) was added a solution of 2,2,2-trifluoroethanol (90 µl, 1.25 mmol, 1.5 equiv) in DMSO (1 ml). The mixture was stirred 15 minutes and 6-chloro-(pyrazin-2-yl)-phenyl-amine (171 mg, 0.833 mmol, 1 equiv) was added as a solution in DMSO (1 ml). The mixture was heated to 80°C for 3 days. The title compound was purified by flash chromatography on silica (19 g, SiO_2), eluted with 25% ethyl acetate-petrol, to afford 110 mg (49%); LCMS 3.95 min, *m/z* $[M+H]^+$ 270.

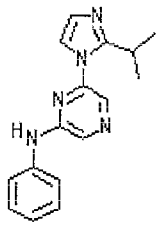
36B. Preparation of (6-Methylsulfanyl-pyrazin-2-yl)-phenyl-amine



The title compound was obtained as a side product of the method of 36A and was isolated as a minor fraction of the reaction products following flash chromatography on silica (19 g, SiO_2), eluting with 25% ethyl acetate-petrol, to afford 3 mg (1%); LCMS 2.76 min, *m/z* $[M+H]^+$ 218.

EXAMPLE 37

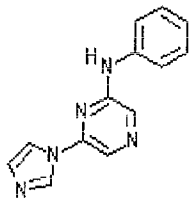
Preparation of [6-(2-Isopropyl-imidazol-1-yl)-pyrazin-2-yl]-phenyl-amine



To sodium hydride (50 mg, 1.25 mmol of a 60% dispersion in oil, 1.5 equiv) in DMSO (1 ml) was added a solution of 2-isopropylimidazole (138 mg, 1.25 mmol, 1.5 equiv) in DMSO (1 ml). The mixture was stirred 15 minutes and 6-chloro-(pyrazin-2-yl)-phenyl-amine (171 mg, 0.833 mmol, 1 equiv) was added as a solution in DMSO (1 ml). The mixture was heated to 80 °C for 3 days then 130 °C for a further 3 days. The title compound was purified by flash chromatography on silica (19 g, SiO_2), eluted with 10% MeOH-CH_2Cl_2, to afford 44 mg (19%); LCMS 2.06 min, *m/z* $[M+H]^+$ 280.

EXAMPLE 38

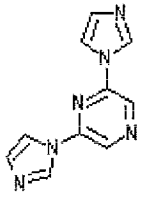
Preparation of 2-(1-Imidazolyl)-6-phenylaminopyrazine



To sodium hydride (50 mg, 1.25 mmol of a 60% dispersion in oil, 1.5 equiv) in DMSO (1 ml) was added a solution of *N*-methanesulfonylimidazole (183 mg, 1.25 mmol, 1.5 equiv) in DMSO (1 ml). The mixture was stirred 15 minutes and 6-chloro-pyrazin-2-yl)-phenyl-amine (171 mg, 0.833 mmol, 1 equiv) was added as a solution in DMSO (1 ml). The mixture was heated to 80 °C for 3 days then 130 °C for a further 3 days. The title compound was purified by flash chromatography on silica (19 g, SiO_2), eluted with 10% MeOH-CH_2Cl_2, to afford 48 mg (20%); LCMS 1.92 min, *m/z* $[M+H]^+$ 238.

EXAMPLE 39

Preparation of 2,6-Bis(1-imidazolyl)pyrazine



To sodium hydride (148 mg, 3.70 mmol of a 60% dispersion in oil, 1.1 equiv) in DMSO (2 ml) was added a solution of imidazole (229 mg, mmol, 1.0 equiv) in DMSO (1 ml). The mixture was stirred for 30 minutes and 2,6-dichloropyrazine (500mg, 3.36 mmol, 1.0 equiv) was added as a solution in DMSO (1 ml). The mixture was heated to 100 °C for 5 hours. The reaction was allowed to cool, quenched with water, extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was purified by flash column chromatography, eluting with 20% EtOAc in petroleum ether, to afford 20 mg (3 %); LCMS 3.02 min, *m/z* $[M+H]^+$ 213.

BIOLOGICAL ACTIVITY

EXAMPLE 40

Measurement of CDK2 Kinase Inhibitory Activity (IC_{50})

Compounds of the invention were tested for kinase inhibitory activity using the following protocol.

1.7 µl of active CDK2/CyclinA (Upstate Biotechnology, 10U/µl) is diluted in assay buffer (250µl of 10X strength assay buffer (200mM MOPS pH 7.2, 250mM β-glycerophosphate, 50mM EDTA, 150mM $MgCl_2$), 11.27 µl 10mM ATP, 2.5 µl 1M DTT, 25 µl 100mM sodium orthovanadate, 708.53 µl H_2O), and 10 µl mixed with 10 µl of histone substrate mix (60 µl bovine histone H1 (Upstate Biotechnology, 5 mg/ml), 940 µl H_2O, 35 µCi γ^{33}P-ATP) and added to 96 well plates along with 5 µl of various dilutions of the test compound in DMSO (up to

2.5%). The reaction is allowed to proceed for 5 hours before being stopped with an excess of ortho-phosphoric acid (30 µl at 2%).

γ^{33}P-ATP which remains unincorporated into the histone H1 is separated from phosphorylated histone H1 on a Millipore MAPH filter plate. The wells of the MAPH plate are wetted with 0.5% orthophosphoric acid, and then the results of the reaction are filtered with a Millipore vacuum filtration unit through the wells. Following filtration, the residue is washed twice with 200 µl of 0.5% orthophosphoric acid. Once the filters have dried, 25 µl of Microscint 20 scintillant is added, and then counted on a Packard Topcount for 30 seconds.

The % inhibition of the CDK2 activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the CDK2 activity (IC_{50}).

The results are shown in Table 3 below.

Table 3

Compound of Example No.	**CDK2 Activity - IC_{50} Values (µM unless stated)**
1	52
2	9
3	7
4	14
5	32
6	4
7	5
8	6
9	9
10	9
11	12

Compound of Example No.	CDK2 Activity - IC_{50} Values (μM unless stated)
12	15
13	23
14	27
15	27
16	24
17	36
18	40
19	43
20	49
21	54
22	60
23	64
24	73
25	98
26	102
27	105
28	16
29	10
30	82
31	17
32	8
33	35
34	68
35	147
36A	17
36B	3
37	12
38	5.5
39	105

PHARMACEUTICAL FORMULATIONS

EXAMPLE 41

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

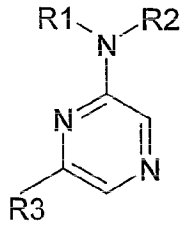
A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A compound of the general formula (I):



(I)

wherein R^1 is selected from hydrogen, cycloalkyl and cycloalkenyl having 3 to 7 ring members; phenyl-C_{1-4} alkyl or a group R^4-A-CH_2- wherein R^4 is selected from amino, mono- or di-C_{1-4} alkylamino, hydroxyl, C_{1-4} alkoxy, SH, $SO_2NR^9R^9$, $CONR^9R^9$, $NR^9SO_2R^{10}$ and NR^9COR^{10}, and A is a C_{1-4} alkylene chain or a group $-(CH_2)_m$-B-$(CH_2)_n$- wherein m and n are each independently 0, 1 or 2 and B is a divalent cycloalkyl or cycloalkenyl group having 3 to 7 ring members; the groups R^9 are the same or different and are each selected from hydrogen, C_{1-4} hydrocarbyl optionally interrupted by O, NR^c, S, SO or SO_2 and optionally substituted by a 5-7 membered carbocyclic or heterocyclic group, or two groups R^9 together with the nitrogen atom to which they are attached form a 5-7 membered heterocyclic group; and R^{10} is hydrogen or C_{1-4} hydrocarbyl optionally interrupted by O, S, SO or SO_2 and optionally substituted by a 5-7 membered carbocyclic or heterocyclic group;

R^2 is selected from aryl and heteroaryl having five to twelve ring members; cycloalkyl and cycloalkenyl having 3 to 7 ring members; a group $(CR^6R^7)_p$-E-R^8 wherein p is 1 or 2, E is a bond, O, S or NR^9, R^6 and R^7 are the same or different and each is hydrogen, C_{1-4} alkyl or phenyl provided that the group $(CR^6R^7)_p$ contains no more than one phenyl group, and R^8 is C_{1-6} hydrocarbyl optionally interrupted by O, NR^c, S, SO or SO_2, a group R^4, phenyl or a mono- or bicyclic heterocyclic group having from five to ten ring members;

or R^1 and R^2 together with the nitrogen atom to which they are attached form a heterocyclic group having 5 to 10 ring members;

R^3 is a substituent selected from halogen, CN, N-linked monocyclic nitrogen-containing heterocyclic groups having from 3 to 7 ring members and containing up to three heteroatoms; and a group R^a-R^b wherein R^a is a bond, O, S, SO or SO_2; and R^b is NR^cR^d or C_{1-4} hydrocarbyl optionally interrupted by O, S, SO, SO_2, NR^c and optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino; and R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl.

2. A compound according to claim 1 wherein R^1 is selected from hydrogen, phenyl-C_{1-4} alkyl, cycloalkyl and cycloalkenyl having 3 to 7 ring members and a group R^4-A-CH_2-.

3. A compound according to claim 2 wherein R^1 is hydrogen.

4. A compound according to any one of claims 1 to 3 wherein R^2 is an aryl group or a heteroaryl group.

5. A compound according to claim 4 wherein R^2 is a phenyl group.

6. A compound according to claim 4 wherein R^2 is a monocyclic or bicyclic heteroaryl group having from 5 to 10 ring members.

7. A compound according to claim 6 wherein R^2 is a monocyclic heteroaryl group having five or six ring members.

8. A compound according to claim 7 wherein the heteroaryl group has one or two heteroatoms which are selected from nitrogen, oxygen and sulphur.

9. A compound according to claim 7 or claim 8 wherein R^2 is a monocyclic heteroaryl group containing one heteroatom ring member.

10. A compound according to claim 7 wherein R^2 is a monocyclic heteroaryl group having five ring members, 1 or 2 of which are heteroatoms selected from nitrogen, oxygen and sulphur, but excluding oxazole, thiazole and imidazole.

11. A compound according to claim 7 wherein the heteroaryl group is selected from pyridyl (e.g. 2-pyridyl and 3-pyridyl), thienyl and pyrazolyl.

12. A compound according to any one of the preceding claims wherein R^2 is an aryl (e.g. phenyl) or heteroaryl group which is unsubstituted or substituted with one or more substituents R^{11} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic or bicyclic carbocyclic or heterocyclic groups having from 3 to 10 ring members (preferably 3 to 7) and containing up to three heteroatoms; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c, NR^cSO_2; R^b is C_{1-8} hydrocarbyl optionally interrupted by O, S, SO, SO_2, NR^c, CO, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; the monocyclic or bicyclic C_{3-10} carbocyclic or heterocyclic groups and R^b being optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, monocyclic carbocyclic or heterocyclic groups having from 3 to 7 ring members and containing up to three heteroatoms; R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl; X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

13. A compound according to claim 12 wherein R^{11} is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino and wherein one or more carbon atoms of the C_{1-8}

hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

14. A compound according to claim 12 or claim 13 wherein the group R^b is an optionally substituted C_{1-8} hydrocarbyl group, and wherein one or more carbon atoms thereof may be optionally replaced as defined in claim 12 or claim 13.

15. A compound according to claim 12 wherein the group R^2 bears one or two substituents (preferably a single substituent group) selected from OH, halogen, C_{1-4} alkyl, $SO_2NR^eR^f$, CO_2H, $CO_2NR^eR^f$, CO_2R^e, NR^eR^g wherein R^e and R^f are each hydrogen or C_{1-4} alkyl groups and R^g is a group R^e or a C_{1-4} alkanoyl group.

16. A compound according to claim 15 wherein the group R^2 is substituted with a group selected from OH, SO_2NH_2, fluorine, chlorine, methyl, carbamoyl, carboxy and acetamido.

17. A compound according to anyone of claims 1 to 3 wherein R^2 is a cycloalkyl and cycloalkenyl group having 3 to 7 ring members.

18. A compound according to claim 17 wherein the cycloalkyl and cycloalkenyl group has 5 or 6 ring members.

19. A compound according to claim 18 wherein R^2 is cyclohexyl.

20. A compound according to any one of claims 1 to 3 wherein R^2 is a group $(CR^6R^7)_p$-E-R^8.

21. A compound according to claim 20 wherein E is a bond.

22. A compound according to claim 20 wherein E is O, S or NR^9.

23. A compound according to claim 22 where E is NR^9.

24. A compound according to any one of claims 20 to 23 wherein R^6 and R^7 are each hydrogen.

25. A compound according to any one of claims 20 to 23 wherein the group $(CR^6R^7)_p$ contains a single phenyl group.

26. A compound according to any one of claims 20 to 25 wherein R^8 is phenyl or a mono- or bicyclic heterocyclic group having from five to ten ring members.

27. A compound according to claim 26 wherein the mono- or bicyclic heterocyclic group is a heteroaryl group.

28. A compound according to claim 27 wherein the heteroaryl group is unsubstituted or substituted with one or more substituents R^{11} as defined in any one of claims 12 to 14.

29. A compound according to claim 27 or claim 28 wherein the heteroaryl group is selected from indole (e.g. indol-5-yl), furyl (e.g. 2-furyl), isoxazolyl (e.g. 5-isoxazolyl), thienyl (e.g. 2-thienyl), pyrazinyl and imidazolyl (e.g. 4-(1H) imidazolyl) groups.

30. A compound according to claim 26 wherein R^8 is a mono- or bicyclic heterocyclic group, the mono- or bicyclic heterocyclic group being a partially or fully saturated group.

31. A compound according to claim 30 wherein R^8 is a non-aromatic heterocyclic group containing up to three heteroatoms selected from nitrogen, sulphur and oxygen.

32. A compound according to claim 31 wherein the heterocyclic group is selected from piperidine, piperazine, N-methylpiperazine, morpholine,

pyrrolidine, imidazoline, imidazolidine, thiazoline, thiazolidine, oxazoline, oxazolidine and tetrahydrofuran.

33. A compound according to claim 32 wherein the non-aromatic heterocyclic group is pyrrolidine.

34. A compound according to any one of claims 4 to 33 wherein R^1 is selected from phenyl-C_{1-4} alkyl; cycloalkyl and cycloalkenyl groups having 3 to 7 ring members; and a group R^4-A-CH_2-.

35. A compound according to claim 34 wherein R^1 is selected from phenyl-C_{1-4} alkyl; and a group R^4-A-CH_2-.

36. A compound according to claim 35 wherein R^1 is a group R^4-A-CH_2-.

37. A compound according to claim 36 wherein A is a C_{1-4} alkylene chain.

38. A compound according to claim 37 wherein A is two or three carbon atoms in length.

39. A compound according to claim 38 wherein A is ethylene or propylene.

40. A compound according to claim 35 wherein A is methylene.

41. A compound according to claim 36 wherein A is a group $-(CH_2)_m$-B-$(CH_2)_n$-.

42. A compound according to claim 41 wherein m and n are both 0 and B is a divalent cycloalkyl group.

43. A compound according to claim 42 wherein B is cyclohexyl.

44. A compound according to any one of claims 36 to 43 wherein R^4 is selected from amino, a hydroxyl group, and a group selected from $SO_2NR^9R^9$, $CONR^9R^9$, $NR^9SO_2R^{10}$ and NR^9COR^{10}.

45. A compound according to claim 44 wherein R^4 is an amino or hydroxyl group.

46. A compound according to claim 45 wherein R^4-A-CH_2- is selected from 3-aminopropyl, 3-hydroxypropyl, 2-hydroxyethyl, and 2-hydroxycyclohexylmethyl.

47. A compound according to claim 44 wherein R^4 is a group $SO_2NR^9R^9$ wherein each R^9 is hydrogen.

48. A compound according to claim 34 wherein R^1 is selected from cycloalkyl and cycloalkenyl groups having 3 to 7 ring members.

49. A compound according to claim 48 wherein the cycloalkyl and cycloalkenyl groups have 5 or 6 ring members.

50. A compound according to claim 49 wherein R^1 is selected from cyclohexyl and cyclopentyl.

51. A compound according to claim 34 wherein R^1 is a phenylethyl or benzyl group.

52. A compound according to claim 51 wherein R^1 is a benzyl group.

53. A compound according to claim 1 wherein R^1 is selected from phenyl-C_{1-4} alkyl or a group R^4-A-CH_2-, and R^2 is a cycloalkyl or cycloalkenyl group having 3 to 7 ring members.

54. A compound according to claim 1 wherein R^1 is hydrogen and R^2 is selected from indolylmethyl (e.g. substituted and unsubstituted 5-indolylmethyl), diphenylmethyl, unsubstituted and substituted thien-2-ylmethyl (e.g. 5-chlorothien-2-ylmethyl), substituted and unsubstituted isoxazolylmethyl (e.g. substituted isoxazol-5-yl such as pyrazinyloxy, substituted isoxazolyl), unsubstituted and substituted furylmethyl (e.g. substituted 2-furylmethyl

such as 5-ethoxycarbonyl-2-furylmethyl) and unsubstituted and substituted imidazolylethyl (e.g. 4-imidazolyl-2-ethyl).

55. A compound according to claim 1 wherein R^1 and R^2 together with the nitrogen atom to which they are attached form a heterocyclic group having 5 to 10 ring members.

56. A compound according to claim 55 wherein the heterocyclic group is monocyclic or bicyclic.

57. A compound according to claim 56 wherein the heterocyclic group is selected from 5-membered monocyclic, 6-membered monocyclic, 5.6-fused bicyclic and 6.6-fused bicyclic groups.

58. A compound according to any one of claims 55 to 57 wherein the heterocyclic group is heteroaryl.

59. A compound according to claim 57 wherein the heterocyclic group is a benzo-fused heterocycle.

60. A compound according to claim 59 wherein the benzo-fused heterocycle is selected from quinoline, isoquinoline, indole and benzimidazole and forms thereof in which the heterocyclic ring is partially or fully reduced.

61. A compound according to claim 56 wherein the heterocyclic group is selected from tetrahydroisoquinoline, benzimidazole, benzimidazolone, piperazine, imidazole, pyrrole and pyrazole.

62. A compound according to any one of the preceding claims wherein R^3 is a halogen, a fluorinated C_{1-4} alkoxy group, a C_{1-4} alkylsulfanyl group, or a five membered nitrogen heterocycle containing 1 or 2 nitrogen atom ring members.

63. A compound according to claim 62 wherein R^3 is chlorine.

64. A compound according to claim 62 wherein R^3 is trifluoroethoxy.

65. A compound according to claim 62 wherein R^3 is methylthio.

66. A compound according to claim 62 wherein R^3 is an imidazolyl group linked to the pyrazine ring through a nitrogen atom.

67. A compound selected from:
2-chloro-6-cyclopentylaminopyrazine;
(6-chloro-pyrazin-2-yl)-phenyl-amine;
6-(3-aminosulphonylphenylamino)-2-chloropyrazine;
5-(2-chloropyrazin-6-ylaminomethyl)-2-methylindole;
2-chloro-6-(2-chlorothiophen-5-ylmethylamino)pyrazine;
N-1-(6-chloro-pyrazin-2-yl)-N-1-cyclohexyl-propane-1,3-diamine;
(6-chloro-pyrazin-2-yl)-pyrrolidin-2-ylmethyl-amine;
3-(6-chloro-pyrazin-2-ylamino)-phenol;
3-(6-chloro-pyrazin-2-ylamino)-thiophene-2-carboxylic acid amide;
4-(6-chloro-pyrazin-2-ylamino)-benzenesulfonamide;
2-{[(6-chloro-pyrazin-2-yl)-cyclohexyl-amino]-methyl}-cyclohexanol;
N-[4-(6-chloro-pyrazin-2-ylamino)-phenyl]-acetamide;
benzhydryl-(6-chloro-pyrazin-2-yl)-amine;
(6-chloro-pyrazin-2-yl)-pyridin-3-yl-amine;
(6-chloro-pyrazin-2-yl)-cyclohexyl-amine;
4-(6-chloro-pyrazin-2-ylamino)-phenol;
5-[(6-chloro-pyrazin-2-ylamino)-methyl]-furan-2-carboxylic acid ethyl ester;
(6-chloro-pyrazin-2-yl)-[3-(6-chloro-pyrazin-2-yloxy)-isoxazol-5-ylmethyl]-amine;
N,N'-bis-(6-chloro-pyrazin-2-yl)-ethane-1,2-diamine;
(6-chloro-pyrazin-2-yl)-(5-methyl-2H-pyrazol-3-yl)-amine;
2-[(6-chloro-pyrazin-2-yl)-cyclohexyl-amino]-ethanol;
2-(6-chloro-pyrazin-2-ylamino)-ethanesulfonic acid amide;
benzyl-(6-chloro-pyrazin-2-yl)-cyclohexyl-amine;

(6-chloro-pyrazin-2-yl)-[2-(1H-imidazol-4-yl)-ethyl]-amine;
2-(6-chloro-pyrazin-2-yl)-1,2,3,4-tetrahydro-isoquinoline;
6'-chloro-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl;
(6-chloro-pyrazin-2-yl)-isobutyl-amine;
(6-chloro-pyrazin-2-yl)-(4-fluoro-phenyl)-amine;
1-(6-chloro-pyrazin-2-yl)-1,3-dihydro-benzoimidazol-2-one;
2-chloro-6-pyrazol-1-yl-pyrazine;
(6-chloro-pyrazin-2-yl)-pyridin-2-yl-amine;
(6-chloro-pyrazin-2-yl)-(5-chloro-pyridin-2-yl)-amine;
1-(6-chloro-pyrazin-2-yl)-1H-benzoimidazole;
6-(6-chloro-pyrazin-2-ylamino)-nicotinic acid;
5-tert-butyl-2-(6-chloro-pyrazin-2-yl)-2H-pyrazol-3-ylamine;
phenyl-[6-(2,2,2-trifluoroethoxy)-pyrazin-2-yl]-amine;
(6-methylsulfanyl-pyrazin-2-yl)-phenyl-amine;
[6-(2-isopropyl-imidazol-1-yl)-pyrazin-2-yl]-phenyl-amine;
2-(1-imidazolyl)-6-phenylaminopyrazine; and
2,6-bis(1-imidazolyl)pyrazine.

68. A compound according to any one of the preceding claims in the form of a salt or solvate.

69. A compound of the formula (I) as defined in any one of claims 1 to 68 for use in the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

70. The use of a compound of the formula (I) as in any one of claims 1 to 68 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase.

71. A method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined in any one of claims 1 to 68.

72. A method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined in any one of claims 1 to 68.

73. A method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound of the formula (I) as defined in any one of claims 1 to 68.

74. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of formula (I) as defined in any one of claims 1 to 68 in an amount effective in inhibiting abnormal cell growth.

75. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of formula (I) as defined in any one of claims 1 to 68 in an amount effective to inhibit cdk2 activity.

76. A compound for use, a use, or a method as defined in any one of claims 69 to 75 wherein the disease state or condition is selected from proliferative disorders such as cancers and conditions such as viral infections, autoimmune diseases and neurodegenerative diseases.

77. A compound for use, a use or a method according to claim 76 wherein the disease state is a cancer selected from breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer, and non-small cell lung carcinomas.

78. A pharmaceutical composition comprising a compound of the formula (I) as defined in any one of claims 1 to 68 and a pharmaceutically acceptable carrier.

79. A compound of the formula (I) as defined in any one of claims 1 to 68 for use in medicine.